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| 09/704,054 | 11/01/2000 | Robert D'Amato | 43170-249244 | 3798 |

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| EXAMINER | |
|---|---|
| ANDERSON, JAMES D | |
| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/704,054 | D'AMATO, ROBERT | |
| | Examiner | Art Unit | |
| | JAMES D. ANDERSON | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 March 2008 and 27 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *23,25-31,33-40,59-62,71 and 72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,25-31,33,35-40,59-62,71 and 72* is/are rejected.

7)☒ Claim(s) *34* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/14/2008 and 5/27/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

***Claims 23, 25-31, 33-40, 59-62, and 71-72 are presented for examination***

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/14/2008 has been entered.

Applicants' amendment filed 3/14/2008 has been received and entered into the application. Accordingly, claim 23 has been amended.

Applicants' arguments have been fully considered and are deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

### *Response to Arguments*

Applicant's arguments, see Response, filed 3/14/2008, with respect to the rejection(s) of claim(s) 23, 25-31, 33-40, 59-62, and 71-72 under 35 U.S.C. 112, 1st Paragraph (Scope of Enablement) have been fully considered and are persuasive. Therefore, the rejection has been

withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of a broader reasonable interpretation of the claims as discussed below.

Independent claim 23, as amended, recites the following method:

> A method for inhibiting the growth of blood-borne tumors in a human comprising administering to said human a therapeutically effective amount of thalidomide to inhibit angiogenesis in said tumor.

The claimed method is thus reasonably interpreted to encompass administering thalidomide to patient in some amount such that the "growth of blood-borne tumors" is "inhibited". This amount of thalidomide is claimed "to inhibit angiogenesis" in said tumors. The instant disclosure does not define "therapeutically effective amount of thalidomide to inhibit angiogenesis", other than to say that for oral administration to humans, a dosage of between 0.1 to 300 mg/kg/day is sufficient (page 21, lines 6-10). It is also noted that dependent claim 27, which depends from claim 23, recites that thalidomide is administered in amount "between approximately 0.1 and approximately 300 mg/kg/day". As such, because the limitations of claim 27 are also inherently present in claim 23, the Examiner is interpreting claim 23 to encompass administration of thalidomide in an amount of "approximately 0.1 mg/kg/day" and up to "approximately 300 mg/kg/day".

In addition, claim 30, which depends from claim 23, recites the limitation wherein "the human is at risk for developing a tumor". This limitation reasonably encompasses a patient population that does not presently have a blood-borne tumor (*e.g.*, prevention). As such, because the limitations of claim 30 are also inherently present in claim 23, the Examiner is interpreting claim 23 to encompass administration of thalidomide to <u>any</u> patient, not only those patients diagnosed as having a blood-borne tumor.

In light of the above claim interpretation, the Examiner is herein reapplying previously cited prior art (Grabstald *et al.*) who teach administration of thalidomide to a patient having multiple myeloma. Applicants have previously argued that Grabstald *et al.* does not provide any evidence of anti-angiogenic activity of thalidomide and further that Grabstald teaches that "no significant degree of antineoplastic activity was demonstrated" (see Response filed 4/19/2007). However, as discussed in M.P.E.P. 2121.01, efficacy is not a requirement for prior art enablement:

> A prior art reference provides an enabling disclosure and thus anticipates a claimed invention if the reference describes the claimed invention in sufficient detail to enable a person of ordinary skill in the art to carry out the claimed invention; "proof of efficacy is not required for a prior art reference to be enabling for purposes of anticipation." *Impax Labs. Inc. v. Aventis Pharm . Inc.*, 468 F.3d 1366, 1383, 81 USPQ2d 1001, 1013 (Fed. Cir. 2006).

Further, it is noted that the instant claims do not recite "treatment" of a patient. Rather, the claims recite "inhibiting the growth of" blood-borne tumors and an amount of thalidomide "to inhibit angiogenesis" in said tumor. As such, because Grabstald administers the same compound (*i.e.*, thalidomide), in amounts that read on the instant claims, to a patient having a blood-borne tumor, the claimed effect (inhibition of growth) and mechanism (inhibition of angiogenesis) must have necessarily occurred in the Grabstald administration method whether the reference recognized that such effects occurred or not.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23, 25-31, 33, 35-40, 59-62, and 71-72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the instant case, the metes and bounds of "blood-borne tumors" cannot be discerned. For example, Applicant appears to distinguish a "solid" tumor from a "blood-borne" tumor (page 9, lines 15-19). In terms of blood-borne tumors, only leukemia is recited as such a tumor (page 9, line 19; claim 34). However, one skilled in the art could interpret "blood-borne tumor" to mean a metastatic tumor that arises in a tissue different from the original primary tumor (*e.g.*, a metastatic breast cancer tumor arising from metastasis of a primary lung cancer tumor). The breast cancer tumor is thus reasonably a "blood-borne" tumor arising from metastasis of lung cancer cells through the blood to the breast. However, such a breast cancer tumor is also now a solid tumor of the breast. Another interpretation of "blood-borne tumor" is that such tumors are limited to hematological malignancies such as leukemia. Applicant's distinction in the disclosure between "solid tumor" and "blood-borne tumor" does not help in interpreting what tumors are and are not "blood-borne tumors" as recited in the claims. For the purposes of examination, the Examiner is interpreting "blood-borne tumors" to mean a hematological malignancies such as leukemia as well as tumors arising from metastasis of solid tumors to other sites.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 23, 25-31, 33, 35-40, and 71-72 are rejected under 35 U.S.C. 102(b) as being anticipated by **Grabstald *et al.*** (Clinical Pharmacology and Therapeutics, 1965, vol. 6, pages 298-302) (previously cited).

Grabstald *et al.* teach administration of thalidomide to 71 patients with advanced metastatic cancer (page 298, right column, "Materials and methods"). One such treated patient was diagnosed with multiple myeloma, a blood-borne tumor as recited in the instant claims (Table I).

With regard to doses, the reference teaches that thalidomide was administered in amounts of 400 mg three times during the day and 800 mg at the hour of sleep for a total dose of 2,000 mg/day[1] (page 299, left column). If this dose was not well tolerated, less was administered. Thus, the amounts of thalidomide administered read on the amounts of thalidomide recited in instant claims 27 and 36 ("between approximately 0.1 and approximately 300 mg/kg/day"), claims 28 and 37 ("between approximately 0.5 and approximately 50 mg/kg/day"), and claims 29 and 38 ("between approximately 1 and approximately 10 mg/kg/day").

While Grabstald does not explicitly teach that thalidomide was orally administered, the expression of doses in "mg", as well as the fact that outpatients were given thalidomide to take on their own ("Some of the subjects who were being treated as outpatients would decrease their drug intake voluntarily..." at page 299, left column), it is reasonable to conclude that thalidomide was orally administered since this was the accepted administration route of thalidomide at the time. Accordingly, Grabstald anticipates the claimed "orally" administered thalidomide as

[1] For an average human weighing 70 kg, this equates to 28.6 mg/kg/day

recited in claims 25, 35, and 71. In addition, oral administration would reasonably be via a tablet or capsule, thus anticipating claims 26, 39, and 72. Tablets and capsules are also reasonably lozenges, thus anticipating claims 31 and 40.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention").

Though Grabstald *et al.* does not expressly teach that thalidomide inhibited multiple myeloma tumor growth or that angiogenesis was inhibited as a result of the administration of thalidomide to the subjects being treated, the administration of the same compound as claimed to the same host (*i.e.*, a human having multiple myeloma) as claimed is considered to necessarily have the claimed effect of inhibiting tumor growth and angiogenesis, whether expressly recognized by Grabstald *et al.* or not. Products of identical chemical composition cannot exert

mutually exclusive properties when administered under the same circumstances or, in the present case, the same host. Please reference MPEP §2112.

Further, it is noted that though Grabstald *et al.* does not expressly teach that the disclosed administration of thalidomide inhibits angiogenesis or tumor growth, it is noted that the very teaching of the administration of the identical compound to that presently claimed must necessarily possess the same inhibition of tumor growth and angiogenesis, even though such properties may not have been appreciated by Grabstald *et al.* at the time of the invention.

It is noted that Grabstald *et al.* did not directly measure tumor growth or angiogenesis. Rather, Grabstald *et al.* evaluated clinical efficacy by gross observations ("...observations relating to the nature and location of the cancer were regularly made in order to demonstrate evidence of therapeutic activity" at page 299, right column). As such, the fact that Grabstald *et al.* did not directly observe an inhibition of tumor or growth or angiogenesis does not mean that such did not occur. In fact, it must have occurred because the same compound was administered in the same amounts to the same patient as instantly claimed.

Though mechanisms of action of chemical entities are no doubt important contributions to scientific and pharmaceutical development, the assessment of patentability under 35 U.S.C. 102 is based upon the therapeutic applications and therapeutic effects of the compounds, not the mechanism by which they exert such a therapeutic effect. Furthermore, it is generally well settled in the courts that a mechanistic property of a chemical compound, or combination of chemical compounds, when administered under identical conditions, is necessarily present, despite the fact that such a property may not have been readily apparent to, or recognized by, one of ordinary skill in the art.

Claims 23, 25-31, and 71-72 are rejected under 35 U.S.C. 102(b) as being anticipated by **Chen *et al***. (Drug Metabolism and Disposition, 1989, vol. 17, pages 402-405) (newly cited).

Chen *et al*. teach oral administration of 200 mg/day thalidomide to healthy male patients (Abstract; page 402, "Subjects and Protocol").

The male volunteers weighed between 55.5 and 87.5 kg. As such, the dose of thalidomide was in the range of 2.3 to 3.6 mg/kg/day which anticipates the claimed dose ranges as recited in claims 27-29.

The male volunteers were in "good health" and thus do not appear to have had tumors. As such, the patient population reads on the claims to the extent that the claims encompass administration to a human "at risk for developing a tumor". As all humans are at some risk of developing a tumor, the male patients in good health taught in Chen *et al*. read on the claims.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc*., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co*., 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and

enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention").

Though Chen *et al.* does not expressly teach that thalidomide inhibited tumor growth or that angiogenesis was inhibited as a result of the administration of thalidomide to the subjects being treated, the administration of the same compound as claimed to the same host (*i.e.*, a human at risk of developing a tumor) as claimed is considered to necessarily have the claimed effect of inhibiting tumor growth and angiogenesis, whether expressly recognized by Chen *et al.* or not. Products of identical chemical composition cannot exert mutually exclusive properties when administered under the same circumstances or, in the present case, the same host. Please reference MPEP §2112.

Further, it is noted that though Chen *et al.* does not expressly teach that the disclosed administration of thalidomide inhibits angiogenesis or tumor growth, it is noted that the very teaching of the administration of the identical compound to that presently claimed must necessarily possess the same inhibition of tumor growth and angiogenesis, even though such properties may not have been appreciated by Chen *et al.* at the time of the invention.

It is noted that Chen *et al.* do not monitor the development of tumor growth or the inhibition of angiogenesis. Rather, Chen *et al.* evaluated the plasma pharmacokinetics and urinary excretion of thalidomide. However, the fact that Chen *et al.* did not directly observe an inhibition of tumor growth or angiogenesis does not mean that such did not occur. In fact, it must have occurred because the same compound was administered in the same amounts to the same patients as instantly claimed.

Though mechanisms of action of chemical entities are no doubt important contributions to scientific and pharmaceutical development, the assessment of patentability under 35 U.S.C. 102 is based upon the therapeutic applications and therapeutic effects of the compounds, not the mechanism by which they exert such a therapeutic effect. Furthermore, it is generally well settled in the courts that a mechanistic property of a chemical compound, or combination of chemical compounds, when administered under identical conditions, is necessarily present, despite the fact that such a property may not have been readily apparent to, or recognized by, one of ordinary skill in the art.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 59-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Grabstald *et al.*** or **Chen *et al.*** as applied to claims 23, 25-31, 33, 35-40, and 71-72, *supra*, in view of **Kaplan *et al.*** (USP No. 5,385,901; Issued Jan. 31, 1995; Filed Oct. 2, 1992) (newly cited).

Grabstald *et al.* and Chen *et al.* teach as applied *supra* and said teachings are applied herein in the same manner and in their entirety. The references do not teach the claimed administration routes or administration forms as recited in claims 59-62.

However, Kaplan *et al.* teach compounds useful for controlling abnormal concentrations of TNF-α in patients (Abstract). The compounds of the invention include thalidomide (Figures

and Examples; Claims). With regard to administration routes and forms, Kaplan *et al.* teach that the compounds of invention can be administered orally in the form of tablets, pills, and lozenges, rectally in the form of a suppository, and parenterally in the form of aqueous solutions or suspensions (col. 10, line 61 to col. 11, line 33).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of the invention to administer thalidomide via any administration known to be useful for such compounds. In this regard, Kaplan *et al.* teach and motivate one skilled in the art to administer compounds such as thalidomide via well known administration routes. As such, one skilled in the art would have been imbued with at least a reasonable expectation of success in formulating a dosage form of thalidomide for administration via the routes instantly claimed.

### *Allowable Subject Matter*

Claim 34 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

### *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614